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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/466,554	06/06/95	SEUBERT	P 15270-002120

020350
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HM12/0320

EXAMINER	
DUFFY, P	
ART UNIT	**PAPER NUMBER**
1645	29

DATE MAILED: 03/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)	
08/466,554	Seubert et al	
Examiner	Group Art Unit	
Duffy	1641	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on Renewal from suspension + review of record.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 42-48 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 42-48 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

Response to Amendment

1. The Group and/or Art Unit of U.S. Patent application S.N. 08/466,554 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Art Unit 1645.

2. The amendments filed 8-11-97 and 10-22-97 have been entered into the record.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. Upon reconsideration of the record, the enablement rejection with respect to claims 43-47 has been reinstated see rejection set forth below.

Rejections Withdrawn

5. In view of a copy of the declaration filed in USSN 08/419,008 on 8-11-97, the art rejections have been withdrawn as to claims 42-48.

New Rejections

Double Patenting

6. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 42-48 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the all the allowed claims of allowed but not yet issued copending Application No. 08/733,202. Although the conflicting claims are not identical, they are not patentably distinct from each other because it is obvious to screen for soluble Aβ(x-≥41) in place of soluble Aβ because Aβ(x-≥41) is a recognized species of soluble Aβ as evidenced by the art of record (Vigo-Pelfry et al).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. It is noted that 08/733,202 has been allowed but has not yet issued as a patent. Therefore, in the event that the '202 application should issue in the interm, the "provisional" status of the rejection will be withdrawn.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 43-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 43 and 44 are drawn to the use of a rodent or mouse that exhibits cerebral deposition of Aβ in a method of screening for a compound to determine its ability to alter the

amount of Aβ (x-≥41). Claims 45-47 are drawn to the use of a transgenic animal model having an expression cassette that drives expression of a sequence which encodes the Swedish mutation of an APP gene and further limit the animal model to a rodent or mouse.

As to claims 43 and 44, the specification fails to teach rodent and mouse models that exhibit cerebral deposition of Aβ for use in the screening assay because it was well established in the art at the time of filing that rodents such as rats and mice did not in fact deposit Aβ in their brain, providing a critical distinction between the human form of Alzheimer's disease and common laboratory rodents (see Joachim et al, Alzheimer Disease and Associated Disorders, 6(1):7-34, 1992, page 20, lines 3-6 in particular). As such claims drawn to the use of rodents that exhibit cerebral deposition of Aβ is clearly not enabled.

As to claims 45-47, the specification fails to provide an enabling disclosure and lacks of an adequate written description on how to make a non-human transgenic animals (including rodents such as a mouse), that specifically exhibit cerebral deposition of Aβ by means of an expression cassette that drives expression of a sequence which encodes the Swedish mutation of an APP gene for use in an *in vivo* screening method for agents which alter the amount of Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF). The is no evidence in the specification or in the art that at the time of filing (November 14, 1994) that cerebral deposition related phenotype could be predictably produced in any transgenic-non-human animal. At the time of filing the production of any transgenic non-human animal that expresses a transgene at a level that affords the mammal a new feature, characteristic or phenotype (i.e. the instant cerebral deposition of Aβ) was still unpredictable. The phenotype of the non-human transgenic animal is a critical claimed feature of the animal model to be used in the method of testing as instantly claimed. The production of transgenic animals having specific pathologies is not routine in the art and requires

a high level of skill, with the ultimate stable expression of the APP gene of interest in germline of the transgenic animal in the appropriate tissue of interest, which also displays cerebral deposition of Aβ and is capable of germline transmission is unpredictable because the integration of the cassette into the genome is random and the stability and degree of expression of the transgene is unpredictable even using strong promoters. This unpredictability in the production of transgenic animals is significantly compounded by the teaching of the art which specifically teach that the generation of transgenic animals displaying the even the β-amyloid deposits in the brain is highly unpredictable and expression is variable (Fukuchi et al, Annals of the New York Academy of Sciences, 1993, pages 217-223) even if the gene is inserted with a expression cassette using the neural-specific enolase promoter. The art at the time of filing recognized that even the production of transgenic mice expressing an APP related transgene is unpredictable as Alzheimer's related pathologies may not form, sufficient expression of the APP transgene may be difficult to achieve, and expression achieve may show an inappropriate tissue distribution (Lanfelt et al, 1993, Behav. Brain Res., 57, page 210, column 1, paragraph 5 and col 2, paragraph 4, lines 8-18). Also, the art teaches that transgenic rats containing an APP transgene failed to demonstrate any Alzheimer's related pathology at six months of age (Felsenstein et al , 1995, Alzheimer's and Parkinson"s Diseases, I. Hanin et al, Plenum Press, New York, page 406, page 1). Thus, it appears that at the time of filing that deficiencies in the specification in providing guidance in the production of transgenic non-human animals including rodents and mice expressing APP or the claimed Swedish variant, sufficient to develop the phenotype of cerebral deposition of Aβ could not have been overcome by a review of the relevant art. Thus, making non-human transgenic animal models providing for the development of cerebral deposition of Aβ using an expression cassette that drives expression of a sequence

which encodes the Swedish mutation of an APP gene is not enabled by the art or the specification or by any post filing evidence. The specification moreover, clearly lacks adequate written guidance as to the description of procedural steps of how to make the expression cassette with the Swedish mutation, what isoform of the APP (695, 751 or 770) is employed, how to make the transgenic animal with this cassette and whether the animal so produced can be predictably reproduced to generate other identical animals and also have the progeny display cerebral deposition of Aβ. Applicants, instead rely on improper incorporation by reference of US application 08/143,697, to use an animal model that has not been established to display cerebral deposition of Aβ. There is no evidence of record or in the art that the claimed APP Swedish variant linked to any mammalian promoter in an any expression cassette will produce Aβ, at sufficient levels to predictably display cerebral deposition of Aβ. Given the complex nature of making transgenic animals, rodents and mice in all possible combinations of the Swedish APP in an expression cassette, it would require undue experimentation for the artisan to implement the claimed invention given the lack of written description in the instant specification for any transgenic animal that predictably and reproducible displayed the pathology of cerebral deposition of Aβ, as is instantly claimed. Given these teaching in the art at the time of filing, the artisan could not have depended on the art to supplement the guidance in the specification in the production of a non-human transgenic animal, rodent or mouse for use in a testing assay to screen for alter the amount of Aβ(x-≥41). Given the unpredictability in the generation of cerebral amyloid deposits in non-human APP transgenic animals, and in view of the lack of adequate written description, and lack of working examples it appears that absent further guidance from applicants, it would require undue experimentation on the part of the skilled artisan to make the non-human transgenic animal carrying the Swedish transgene that provides predictable and

reproducible cerebral deposition of Aβ, for use in an *in vivo* screening method for agents which alter the amount of Aβ (x -≥ 41) peptide in the cerebrospinal fluid (CSF).

Applicants have previously argued the PDAPP mouse is present in the art and displays cerebral deposition of amyloid as evidenced by Games et al (Nature 373:523, 1995) and Hsiao et al. (Science 274:99, 1996). This is not persuasive, because claims are not limited to the PDAPP mouse, nor the construct that was used to produce the PDAPP mouse. Moreover, the references do not exemplify the state of the art at the time of the instant invention because they were published 1-2 years after the filing date of the instant application and they rely on information that was not available at the time of the instant invention (priority accorded under 35 USC § 120 is November 14, 1994). See *In re Wright*, 27 USPQ 1510, 1514 (Fed. Cir. 1993) (developments occurring after the filing date are of no consequence regarding what one skilled in the art believed as of the filing date). As such, the enablement rejection with respect to claims 45-47 as drawn to how to make non-human transgenic animals that exhibit cerebral deposition of Aβ for use the method of screening as claimed is reinstated.

Status of Claims

10. Claims 42-48 are rejected.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to

reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
March 19, 2001

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600